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# **NeuroChip, an updated version of the NeuroX genotyping platform to rapidly screen for variants associated with neurological diseases**

Cornelis Blauwendraat<sup>1,\*</sup>, Faraz Faghri<sup>2,3\*</sup>, Joshua T. Geiger<sup>1</sup>, Mike A. Nalls<sup>2,4</sup>, Aude Nicolas<sup>2</sup>, Yevgeniya Abramzon<sup>2</sup>, Natalie A. Murphy<sup>2</sup>, J. Raphael Gibbs<sup>2</sup>, Mina Ryten<sup>5</sup>, Raffaele Ferrari<sup>5</sup>, Henry Houlden<sup>5</sup>, Lasse Pihlstrom<sup>5,6,7</sup>, Julie Williams<sup>8</sup>, Huw R. Morris<sup>9</sup>, Steven Lubbe<sup>9,10</sup>, Dena G. Hernandez<sup>2,11</sup>, Kin Y. Mok<sup>5,12</sup>, Jose Bras<sup>5</sup>, Rita Guerreiro<sup>5</sup>, Roy H. Campbell<sup>3</sup>, Bryan J. Traynor<sup>2</sup>, Ruth Chia<sup>2</sup>, Javier Simón-Sánchez<sup>11,13</sup>, COURAGE-PD Consortium, Laurie Robak<sup>14</sup>, Joshua Shulman<sup>14</sup>, Ekaterina Rogaeva<sup>15,16</sup>, John A. Hardy<sup>5</sup>, Andrew B. Singleton<sup>2</sup>, Sonja W. Scholz<sup>1,17,†</sup>, on behalf of the International Parkinson's Disease Genomics Consortium (IPDGC)

\* these authors contributed equally

<sup>1</sup> Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

<sup>2</sup> Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA

<sup>3</sup> Department of Computer Science, University of Illinois at Urbana-Champaign, Urbana, IL, USA

<sup>4</sup> Founder/Consultant with dataconsult.io, Glen Echo, MD, USA

<sup>5</sup> Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK

<sup>6</sup> Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

<sup>7</sup> Department of Neurology, Oslo University Hospital, Oslo, Norway

<sup>8</sup> Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK

<sup>9</sup> Department of Clinical Neuroscience, UCL Institute of Neurology, Queen Square, London, UK

<sup>10</sup> Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

<sup>11</sup> German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany

<sup>12</sup> Division of Life Science, Hong Kong University of Science and Technology, Hong Kong SAR, China

<sup>13</sup> Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

<sup>13</sup> Department of Neurology, Baylor College of Medicine, Houston, TX, USA

<sup>14</sup> Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

<sup>15</sup> Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada

<sup>16</sup> Department of Medicine, Division of Neurology, University of Toronto, Toronto, Ontario, Canada

<sup>17</sup> Department of Neurology, Johns Hopkins University Medical Center, Baltimore, MD, USA

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**Corresponding author:** Sonja W. Scholz, M.D. Ph.D., Neurogenetics Branch, NINDS | National Institutes of Health; 35 Convent Drive, Bethesda, MD 20892, USA; email: [sonja.scholz@nih.gov](mailto:sonja.scholz@nih.gov)

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## **Abstract**

Genetics has proven to be a powerful approach in neurodegenerative diseases research, resulting in the identification of numerous causal and risk variants. Previously, we introduced the NeuroX Illumina genotyping array, a fast and efficient genotyping platform designed for the investigation of genetic variation in neurodegenerative diseases. Here, we present its updated version, named NeuroChip. The NeuroChip is a low cost, custom-designed array containing a tagging variant backbone of about 306,670 variants complemented with a manually curated custom content comprised of 179,467 variants implicated in diverse neurological diseases, including Alzheimer's disease, Parkinson's disease, Lewy body dementia, amyotrophic lateral sclerosis, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration and multiple system atrophy. The tagging backbone was chosen because of the low cost and good genome-wide resolution; the custom content can be combined with other backbones, like population or drug development arrays. Using the NeuroChip, we can accurately identify rare variants and impute over 5.3 million common SNPs from the latest release of Haplotype Reference Consortium. In summary, we describe the design and usage of the NeuroChip array, and show its capability of detecting rare pathogenic variants in numerous neurodegenerative diseases. The NeuroChip has a more comprehensive and improved content, which makes it a reliable, high-throughput, cost-effective screening tool for genetic research and molecular diagnostics in neurodegenerative diseases.

## 1. Introduction

Neurodegenerative diseases are a major burden to the aging world population and currently these diseases are incurable and irreversible. Common and rare genetic alterations in many genes have been identified as disease-causing or contributing to the development of neurodegeneration (Naj et al., 2017, Singleton and Hardy, 2016). To date, there are four main uses of genetics: 1) to confirm a clinical diagnosis by identifying a causal mutation, 2) to identify risk variants and disease modifiers that influence risk for disease, 3) to increase knowledge of the molecular pathobiology of disease in the hopes of identifying therapeutic targets, and 4) to improve patient selection for pathway-specific clinical trial design. A reliable, high-throughput and cost-effective platform that can rapidly conduct these functions could therefore be immensely valuable to the field.

Previously, we presented the NeuroX array, which was a collaborative effort with the objective of designing a genotyping platform that would allow rapid genetic characterization of samples in the context of genetic mutations and risk factors associated with common neurodegenerative diseases (Nalls et al., 2015). This was an exonic array (or exome chip) based on the Infinium HumanExome Beadchip v1.1 containing 242,901 exome-focused variants as well as 24,706 custom variants focusing on neurological diseases. The NeuroX array has already been successfully used in dozens of studies (Barber et al., 2017, Carrasquillo et al., 2016, Ghani et al., 2015, Nalls et al., 2016, Rosenthal et al., 2016). However, due to the backbone's focus on rare exonic variation, common non-exonic variants were largely missed, resulting in a modest genome-wide resolution and only partial capture of the known low frequency exonic variation.

Additionally, the number of genotype-phenotype associations and pathogenic variants keeps expanding, so there was a continued need for updating this useful platform.

Here, we report on an updated version of NeuroX, named NeuroChip. The NeuroChip backbone is based on a genome-wide genotyping array (Infinium HumanCore-24 v1.0) containing 306,670 tagging variants and a custom content that has been updated and extended with neurodegenerative disease-related custom content consisting of 179,467 variants. This backbone was chosen because of the low cost and good genome-wide resolution. This backbone is flexible and other arrays can be used with this custom content, such as population or drug development arrays (Infinium Multi-Ethnic, Infinium DrugDev). The NeuroChip allows to accurately identify rare neurodegenerative candidate variants and impute over 5.3 million common variants. Its approximate cost of ~\$40 per sample is a fraction of the price of next-generation whole exome or whole genome sequencing, and therefore provides a valuable, high-throughput screening tool for loci and variants implicated in neurodegenerative diseases. Further, this array can be used as a tool to prioritize samples for more expensive genome sequencing approaches.

## **2. Methods**

### **2.1 NeuroChip array design**

The backbone of the array, the Infinium HumanCore-24 v1.0, contains 306,670 highly informative tagging SNPs which can be used for high-throughput and high-quality imputation of genome-wide variants across diverse populations (Illumina). In addition, the chip contains 179,467 custom disease-associated variants (Table 1) covering neurodegenerative diseases including: Alzheimer's disease (AD), Parkinson's disease (PD), Lewy body dementia (LBD), frontotemporal dementia

(FTD), amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). The custom-content has been curated by members of the International Parkinson's Disease Genomics Consortium (IPDGC) to include common variants and rare mutations implicated in neurological diseases as reported in the Human Gene Mutation Database (HGMD Professional 2016.4, QIAGEN), the NHGRI GWAS Catalog (<https://www.ebi.ac.uk/gwas/>), the Parkinson's Disease Mutation Database (<http://www.molgen.vib-ua.be/PDMutDB>), the Alzheimer's Disease and Frontotemporal Dementia Database (<http://www.molgen.ua.ac.be/admutations/>), and based on literature review as well as own data; particularly in the latter case, collaborators submitted variants that were identified in multiple ongoing (or completed) unpublished projects, including variants from genome-wide association (GWA), whole exome, whole genome, targeted sequencing studies and systems biology studies. See Supplementary Table 1 for the complete content of the NeuroChip array.

## **2.2 NeuroChip array genotyping**

We genotyped a cohort of 273 neurologically normal controls as per the manufacturer's instructions (Illumina) to generate pilot NeuroChip data. These samples have been collected by the North American Brain Expression Consortium (NABEC) and described elsewhere (Hernandez et al., 2012). In total, 183 males and 90 females were included. All subjects reported European ancestry and had no neurological disease based on pathological evaluation. All samples were obtained from North American brain banks. To assess the reproducibility of the NeuroChip, we genotyped 15 samples twice in separate experiments.

Raw data files were imported into GenomeStudio (version 2.0, Illumina). For initial quality control, we confirmed accurate, high quality genotyping using a call rate threshold of > 95%. We reclustered the samples using a GenCall threshold of 0.15 and recalled all variants. The genotyping cluster file based on ~3,500 individuals of ongoing projects is available in the Supplementary Materials (Supplementary File 1). The mean call rate post-reclustering was 0.992 (range: 0.954-0.995). The data were exported from GenomeStudio using the Illumina-to-PLINK module 2.1.4 and imported into PLINK (version 1.90) (Chang et al., 2015). Next, we checked individuals for discrepancies between reported sex and genotypic sex, cryptic relatedness (PIHAT <0.05), and heterogeneity contamination, and found that no samples failed this quality control step. Genotype data of the 273 neurologically normal controls are deposited in the European Genome-Phenome Archive under submission number **EGAS00000XXX**.

### **2.3 NeuroChip content annotation**

Annotation of the NeuroChip content was performed using ANNOVAR (Wang et al., 2010). For each variant, a gene-based annotation, *in silico* impact scores, and frequencies from public databases were obtained. To predict the impact scores, the following algorithms were used: SIFT (Kumar et al., 2009), Polyphen-2 (Adzhubei et al., 2010), and CADD (Kircher et al., 2014). Population frequencies were obtained from the Exome Aggregation Consortium (version 0.3.1) (<http://exac.broadinstitute.org/>) containing 60,706 individuals. Additionally, all variants were investigated for their presence in the Human Gene Mutation Database (HGMD, accessed 20 December 2016). Variants associated with a common neurodegenerative syndrome (AD, ALS, FTD and PD) were manually curated and are summarized in Supplementary Table 2.



## **2.4 NeuroChip content imputation**

After confirming high-quality genotyping (call rate >95%) and European ancestry in all individuals (based on 1000Genomes clustering) (Genomes Project et al., 2015), we performed imputation using the Michigan imputation server, according to established guidelines (<https://imputationserver.sph.umich.edu>) (Das et al., 2016). In brief, genotypes were prepared for imputation using provided scripts (HRC-1000G-check-bim.pl), which compares variant ID, strand, and allele frequencies to the haplotype reference panel (HRC version r1.1, April 2016) (McCarthy et al., 2016). A total of 332,015 autosomal SNPs were submitted to the Imputation Server using ShapeIT (v2.r790).

## **2.5 *APOE* allele genotyping**

To determine the accuracy of *APOE* allele predictions, we performed Taqman genotyping of two nonsynonymous *APOE* SNPs (rs7412 and rs429358) on an Applied Biosystems ViiA 7 Real-Time PCR System using an established protocol (Federoff et al., 2012). 272 out of 273 control samples had sufficient DNA for genotyping. Allelic discrimination was conducted using QuantStudio software (version 1.3, Thermo Fisher Scientific, Carlsbad, CA, USA). Taqman genotype results were then compared to the corresponding results for the same SNPs generated using the NeuroChip. Given the importance of *APOE*, NeuroChip was designed so that rs7412 is genotyped by four separate probes (three of which performed well: rs7412, seq-rs7412-B1, seq-rs7412-B3). Similarly, rs429358 was genotyped by five separate bead probes (two of which performed well:

seq-rs429358-T2, seq-rs429358-T3). This redundancy ensures accurate APOE genotyping by the NeuroChip platform.

### **3. Results**

#### **3.1 NeuroChip content overview**

In total, the NeuroChip array contains 473,442 autosomal variants, 11,840 sex chromosomal variants, and 160 mitochondrial variants. Additionally, 16,274 NeuroChip variants detect small insertions or deletions (Table 1). The overlap between NeuroX and NeuroChip is small (n= 19,289 variants) due to the difference in the design of the backbone; the NeuroX array is focused on exonic content, whereas the NeuroChip is focused on genome wide tagging content.

#### **3.2 NeuroChip pathogenic variant content**

In total, the NeuroChip harbors 8,086 disease-associated variants that are included in HGMD, a professionally curated database of published genetic variants that have been linked to inherited human diseases (neurological and non-neurological). The NeuroChip HGMD content includes 1,233 variants (1,202 SNPs and 31 indels) linked to common neurodegenerative syndromes (see Supplementary Figure 1 for a comparison between NeuroX and NeuroChip). In this content, after manually curation, 601 variants are associated with ALS or FTD, 348 with PD, and 284 with AD. Figure 1 shows the number of pathogenic variants per gene covered in common neurodegenerative syndromes. Detailed, manually curated and annotated variant lists for the abovementioned neurodegenerative disease categories are documented in Supplementary Table

2. These annotated lists can be used as filters to quickly screen for known mutations and risk variants.

### **3.3 NeuroChip genotyping results**

#### *Genotyping reproducibility*

Of the 15 technical replicates, all samples yielded high quality, reproducible genotyping results. The mean concordance rate per technical replicate was 0.9996 (range=0.9991-0.9999); on average, 190 variants (range=27-435) differed per technical replicate (0.04% of the total included variants on the array). Across the 15 technical replicates, 1,978 unique variants were discordant, of which 749 (37.9%) were from the backbone and 1,229 (62.1%) were from the custom content (Supplementary Table 3).

#### *Imputation*

Imputation of autosomal variants was performed on a series of 273 European descent individuals using the haplotype reference panel (McCarthy et al., 2016) containing 39,235,157 variants, all with an estimated minor allele count of  $\geq 5$  in 32,488 individuals. Initial pre-imputation filtering of the NeuroChip data (including removing duplicates and non-overlapping variants, switch strands, and updating position) resulted in 332,015 variants. After imputation, 11,879,345 variants were obtained with an imputation  $R^2$  of  $> 0.30$ . Filtering based on  $MAF > 0.05$ , Hardy-Weinberg Equilibrium  $p$ -value of  $> 1e-6$  resulted in 5,316,028 variants. In this imputed dataset,

we successfully and reliably identified 22 of 26 PD risk alleles and 19 of the 21 AD GWA SNPs (Lambert et al., 2013, Nalls et al., 2014).

#### *Genotype accuracy*

GenTrain scores were calculated for all NeuroChip variants using GenomeStudio (version 2, Illumina). The GenTrain score is a statistical score based on the shapes of the different allelic clusters and their relative distance to each other (Illumina). Typically, GenTrain scores > 0.7 are considered high quality genotypes. Previously, GenTrain scores of the NeuroX showed that genotyping quality in the custom content was lower compared to the backbone (Nalls et al., 2015). However, preliminary NeuroChip data from several ongoing projects (based on ~3,500 individuals) reveals that the backbone and the custom content have a high comparable average score (0.819 and 0.820, respectively), indicating high genotyping accuracy (Supplementary Figures 2 & 3).

#### *Validation of APOE genotyping*

*APOE* alleles are important genetic risk factors for both AD and LDB, but genotyping of this region is complicated by high GC content (Singleton et al., 2002, Strittmatter and Roses, 1996). For this reason, we chose to validate the accuracy of *APOE* allele genotyping by comparing Taqman results with genotype predictions from the NeuroChip (Supplementary Table 4). Taqman genotyping for rs7412 and rs429358 was successful in all 272 samples. NeuroChip genotyping for both SNPs was successful in 265 out of these 272 controls (97.4%). Five samples were discordant for *APOE* allele genotyping between Taqman and NeuroChip, representing 1.9% of our test

cohort (n = 265 samples). The performance of the NeuroChip for *APOE* genotyping was significantly better than the original NeuroX platform, which was unable to reliably detect rs7412 and rs429358 genotypes (Ghani et al., 2015, Nalls et al., 2015).

#### **4. Discussion**

The main goal was to develop a genotyping array that allows a rapid, high-throughput identification of common and rare single nucleotide variants in the human genome. Affordable screening of large cohorts for disease-associated variants allows for testing of polygenic inheritance that could explain the diversity of clinical and pathological characteristics of neurodegenerative diseases. NeuroChip genotyping is currently much faster and cheaper than next-generation sequencing methods. The NeuroChip is estimated to cost ~ \$40/sample, which is currently less than ~ 10% and ~ 5% of the cost of whole exome sequencing and whole genome sequencing, respectively.

We have designed, implemented and validated the NeuroChip array platform for high throughput genotyping. However, it is important to recognize the limitations of this approach. Like all genotyping arrays, NeuroChip does not detect novel sequence changes. It is also not possible to genotype variants in complex genomic regions (e.g. due to pseudogenes) or to identify repeat expansions due to the difficulty in designing reliable probes. Nevertheless, every effort was made to improve genotyping calling in NeuroChip. For example, it was recognized that the *APOE* locus performed poorly on the original NeuroX platform (Ghani et al., 2015). Given the importance of this genomic region in neurodegeneration, the revised NeuroChip probe design included multiple

probes for SNPs in this region. This led to reliable *APOE* allele calling with a concordance rate of 98.1% between NeuroChip and Taqman.

In conclusion, we describe the design and usage of the NeuroChip array, which has a more comprehensive and improved content compared to NeuroX. We discussed its capability of detecting rare variants associated with numerous neurodegenerative diseases and demonstrated that imputation of the NeuroChip content results in a high and robust genome-wide common variant coverage.

### **Disclosure statement**

Dr. Mike A. Nalls' participation is supported by a consulting contract between dataconsult.io LLC and the National Institute on Aging, NIH, Bethesda, MD, USA, as a possible conflict of interest Dr. Nalls also consults for Illumina Inc, the Michael J. Fox Foundation and University of California Healthcare.

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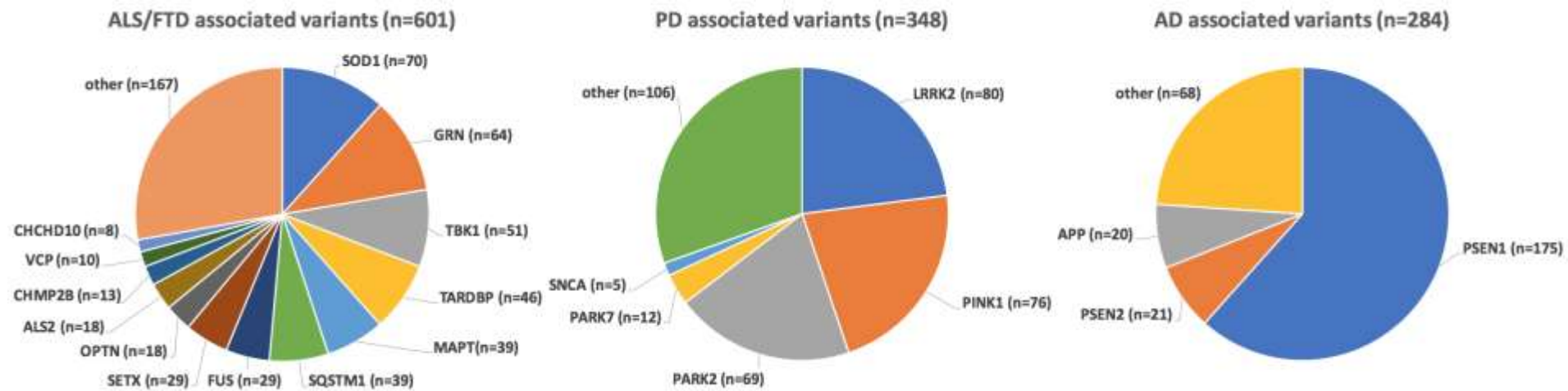
## TABLES AND FIGURES

**Table 1. Differences between NeuroX and the NeuroChip.**

Variant Description	NeuroX	NeuroChip	Comparison
Total variants (pre-QC)	267,607	486,137	+218,530
Backbone	242,901	306,670	+63,769
Custom-content variants	24,706	179,467	+154,761
Indels	200	16,259	+16,059
Autosomal variants	261,477	473,442	+211,965
Coding variants	226,104	88,560	-137,544
Sex chromosomal variants	5,906	11,840	+5,934
Mitochondrial variants	219	160	-59
Variants with MAF < 0.05	219,093	227,448	+8,355
Variants with MAF < 0.001	179,500	154,953	-24,547

MAF = minor allele frequency

**Figure 1.**



**Overview of the number of HGMD disease associated variants that are present on the NeuroChip.** AD = Alzheimer's disease, ALS = amyotrophic lateral sclerosis, FTD = frontotemporal dementia, and PD = Parkinson's disease

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Supplementary File 1: Genotyping Cluster File	-> see attached <a href="#">NeuroChip.egt</a> file

### **IPDGC consortium members and affiliations:**

Alastair J Noyce (Department of Molecular Neuroscience, UCL, London, UK), Alexis Brice (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Anamika Giri (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), Angelika Oehmig (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), Arianna Tucci (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Aude Nicolas (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Claudia Schulte (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research), Mark R Cookson (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA), Cornelis Blauwendraat (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA), Demis Kia (UCL Genetics Institute; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Fabrice Danjou (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Faraz Faghri (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA; Department of Computer Science, University of Illinois at Urbana-Champaign, Urbana, IL, USA), Gavin Charlesworth (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), J Raphael Gibbs (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Huw R Morris (National Hospital for Neurology and Neurosurgery, University College London, London, UK), Helene Plun-Favreau (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Dena G Hernandez (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Peter Holmans (Biostatistics & Bioinformatics Unit, Institute of Psychological Medicine and Clinical Neuroscience, MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff, UK), Huw R Morris

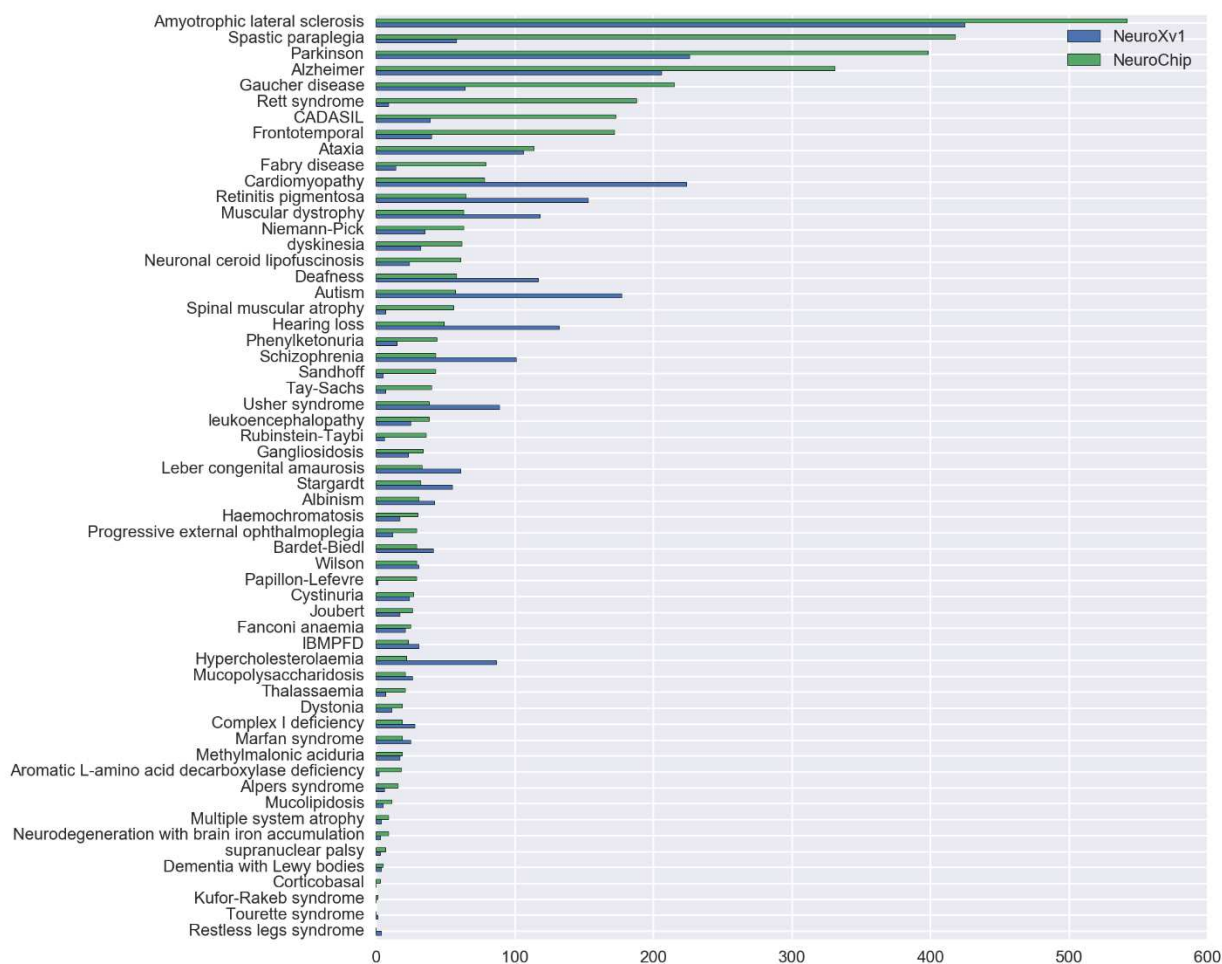
(National Hospital for Neurology and Neurosurgery, University College London, London, UK), Iris Jansen (VU University Medical Center, Amsterdam, Netherlands), John Hardy (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Javier Simón-Sánchez (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), Jose M Bras (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Joshua M. Shulman (Baylor College of Medicine, Houston, Texas, USA), John Quinn (Institute of Translational Medicine, University of Liverpool, Liverpool, UK), Juan A. Botía (Universidad de Murcia, Murcia, Spain), Kin Y Mok (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Kimberley Billingsley (Institute of Translational Medicine, University of Liverpool, Liverpool, UK), Lasse Pihlstrom (Department of Neurology, Oslo University Hospital, Oslo, Norway), Lea R'Bibo (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Codrin Lungu (National Institutes of Health Parkinson Clinic, NINDS, National Institutes of Health, Bethesda, MD, USA), Manu Sharma (Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tübingen and Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen Germany), Maria Martinez (INSERM UMR 1220; and Paul Sabatier University, Toulouse, France), Mina Ryten (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Valentina Escott-Price (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK), Niccolo E. Mencacci (Department of Molecular Neuroscience, UCL, London, UK), Mike A. Nalls (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA; Contractor/consultant with Kelly Services, Rockville, MD, USA), Nicholas W Wood (UCL Genetics Institute; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Patrick Lewis (University of Reading, Reading, UK), Paul Denny (University College London, London, UK), Peter Heutink (DZNE, German Center for Neurodegenerative Diseases and Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany), Patrizia Rizzu (DZNE, German Center for Neurodegenerative Diseases), Pille Taba (Department of Neurology and Neurosurgery, University of Tartu, Tartu, Estonia), Rita Guerreiro (Department of Molecular

Neuroscience, UCL Institute of Neurology, London, UK), Ruth Lovering (University College London, London, UK), Raquel Duran Ogalla (University College London, London, UK), Rebecca Foulger (University College London, London, UK), Laurie Robak (Baylor College of Medicine, Houston, Texas, USA), Steven Lubbe (Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA), Steven Finkbeiner (Departments of Neurology and Physiology, University of California, San Francisco; Gladstone Institute of Neurological Disease; Taube/Koret Center for Neurodegenerative Disease Research, San Francisco, CA, USA), Sigurlaug Sveinbjörnsdóttir (Department of Neurology, Landspítali University Hospital, Reykjavík, Iceland; Department of Neurology, MEHT Broomfield Hospital, Chelmsford, Essex, UK; and Queen Mary College, University of London, London, UK), Andrew B Singleton (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Sonja Scholz (Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA), Sulev Koks (Department of Pathophysiology, University of Tartu, Tartu, Estonia), Suzanne Lesage (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Jean-Christophe Corvol (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, Centre d'Investigation Clinique Pitié Neurosciences CIC-1422, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Thomas Foltynie (UCL Institute of Neurology, London, UK), Thomas Gasser (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), T. Ryan Price (University California Irvine, Irvine, CA, USA), Una-Marie Sheerin (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Nigel Williams (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff, UK), Xylena Reed (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA).

**COURAGE-PD Consortium members:**

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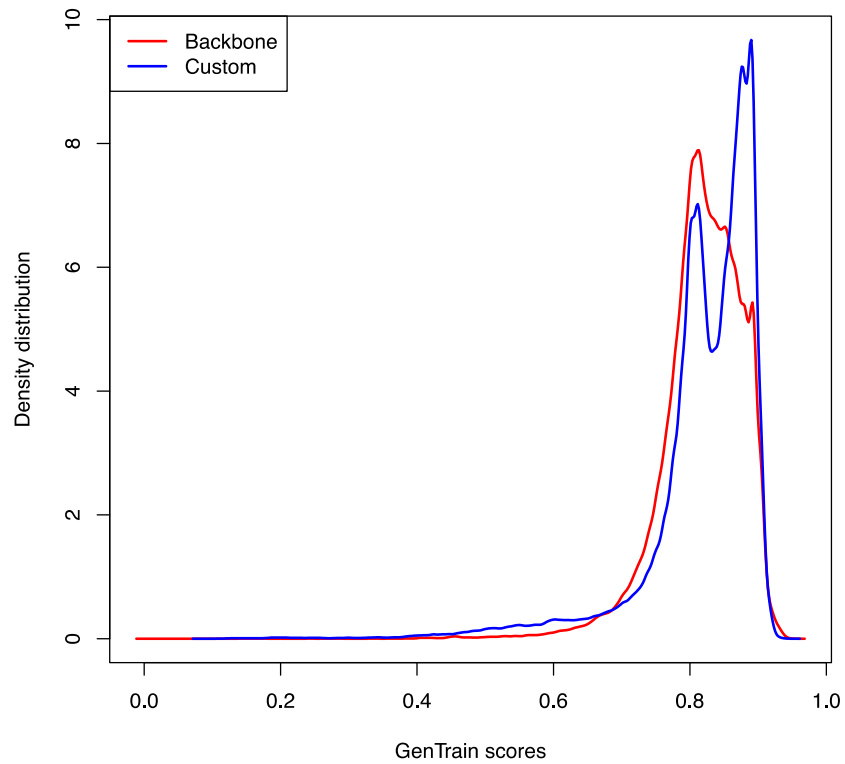
**Supplementary Figure 1.**



**Comparison between NeuroX and NeuroChip HGMD phenotypes.** The content of both NeuroX and NeuroChip was compared with the HGMD database (December, 2016). Phenotypes of included variants were binned in groups and compared between NeuroX and NeuroChip. Here you can see a clear increase in neurodegenerative disease content.



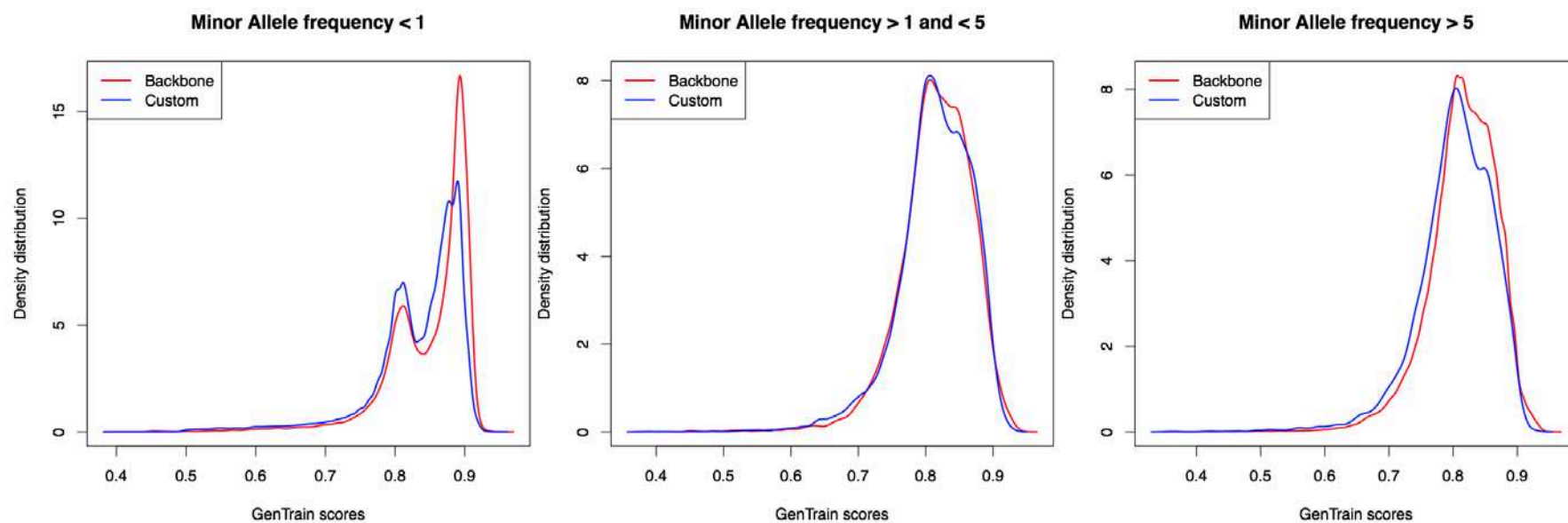
**Supplementary Figure 2.**



**GenTrain scores of the NeuroChip separated by variant origin (backbone or custom content).**

Variants on the backbone are represented in red and variants on the custom content are represented by the blue line. This graph demonstrates high genotyping accuracy.

**Supplementary Figure 3.**



**GenTrain scores of the NeuroChip separated by variant origin (backbone or custom content) and divided by minor allele frequency.**

NeuroChip variant were divided in three group by minor allele frequency (MAF): larger than 5%, between 5-1% and lower than 1%.

Variants on the backbone are represented in red and variants on the custom content are represented by the blue line.

## Supplementary Table 2: Detailed, mar

NeuroChip\_variant\_location\_hg19  
NeuroChip\_variant\_name  
NeuroChip\_variant\_name\_duplicates  
HGMD\_dbSNP\_rsID  
HGMD\_record\_ID  
HGMD\_Ref\_Allele  
HGMD\_Alt\_Allele  
HGMD.Associated\_disease/phenotype  
HGMD.Mutation\_Category  
HGMD.Codon\_Change  
HGMD.Amino\_Acid\_Change  
HGMD.Codon\_Number  
ANNO\_Func.refGene  
ANNO\_Gene.refGene  
ANNO\_AAChange.refGene  
ANNO\_PopFreqMax  
ANNO\_SIFT\_pred  
ANNO\_Polyphen2\_HVAR\_pred  
ANNO\_CADD\_phred

## Manually curated and annotated potential pathogen

Location of the NeuroChip variant based on hg19 genome

Name of the NeuroChip variant

Names of the duplicate NeuroChip variant (when applicable)

dbSNP number obtained from HGMD database

Record number obtained from HGMD database

Reference allele obtained from HGMD database

Alternative allele obtained from HGMD database

Associated disease/phenotype obtained from HGMD database

Mutation category obtained from HGMD database -> e.g. splicing, intron

Codon change obtained from HGMD database

Amino acid change obtained from HGMD database

Codon number that is changed due to variant obtained from HGMD

Type of variant based on the annotated transcripts in RefSeq Gene

Gene-name based on the annotated transcripts in RefSeq Gene

Amino acid change based on the annotated transcripts in RefSeq Gene

A database containing the maximum allele frequency from 1000G, E

SIFT scores -> D: Deleterious (sift<=0.05); T: tolerated (sift>0.05)

Polyphen2 HVAR scores -> D: Probably damaging (>=0.909), P: possible

Combined Annotation Dependent Depletion phred scores, scores higher

## ic variant list

indel, missense

database

from ANNOVAR database -> e.g. splicing, indel, missense

n ANNOVAR database

gene from ANNOVAR database

SP6500, ExAC and CG46 from ANNOVAR

bly damaging ( $0.447 \leq \text{pp2\_hdiv} \leq 0.909$ ); B: benign ( $\text{pp2\_hdiv} \leq 0.446$ )  
gher than 20 are considered potential pathogenic

## Supplementary Table 3: List of discordant variants ob

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11:63670247  
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13:111155774  
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15:62360405  
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16:18882730-18882730:C  
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16:30733985  
16:57847634:indel  
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rs7568035  
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rs75950479  
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rs9743901  
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rs988345  
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rs9918914  
rs992642  
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rs9953734  
rs997542  
rs9979663  
rs998257  
rs9997921  
seq-ADES601  
seq-ADES604  
seq-prion1653  
seq-prion2248  
seq-prion2397  
seq-prion2451  
seq-prion570  
variant.105446  
variant.11006  
variant.47000  
variant.71418  
variant.73621  
variant.77278



variant.80031

**tained from the 15 technical replicates**

## Supplementary Table 4. *APOE* genotype compa

FID

NeuroChip\_ID

The NeuroChip identifier

NABEC\_ID

The previously assigned NABEC ID based on (Hernande

call\_rate\_(post\_reclustering)

Overall genotyping call rate

Gender

Gender

Taqman APOE

APOE allele status based on Taqman assay

NeuroChip APOE

APOE allele status based on NeuroChip array

Comparison

Comparison between the APOE allele genotypes

seq-rs429358-T2

Genotype call of probe seq-rs429358-T2, note that 0/0

seq-rs429358-T3

Genotype call of probe seq-rs429358-T3, note that 0/0

consensus\_rs429358

Consensus of rs429358 based on seq-rs429358-T2 and

rs7412

Genotype call of probe rs7412, note that 0/0 means th

seq-rs7412-B1

Genotype call of probe seq-rs7412-B1, note that 0/0 m

seq-rs7412-B3

Genotype call of probe seq-rs7412-B3, note that 0/0 m

consensus\_rs7412

Consensus of rs7412 based on rs7412, seq-rs7412-B1 a

# Comparison between Taqman and NeuroChip array

z et al., 2012) and dbGAP record phs000249

means that no genotype was called

means that no genotype was called

seq-rs429358-T3

at no genotype was called

means that no genotype was called

means that no genotype was called

and seq-rs7412-B3